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NOTICE OF ALLOWANCE AND ISSUE FEE DUE

12M2/0610

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APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
08/464,792	06/06/95	080	DAHLEN, B 1203	06/10/97
First Named Applicant	D'AMATO,	ROBERT		

TITLE OF INVENTION METHODS AND COMPOSITIONS FOR INHIBITION OF ANGIOGENESIS

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 05213-0113	514-323.000	001	UTILITY	NO	$1290.00	09/10/97

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.
If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status, or
B. If the status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

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B. File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

II. Part B of this notice should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "6b" of Part B should be completed.

III. All communications regarding this application must give application number and batch number. Please direct all communication prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

Notice of Allowability

Application No.	Applicant(s)
08/468,792	D'Amato
Examiner	**Group Art Unit**
Garth M. Dahlen	1203

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course.

☒ This communication is responsive to *the amendment filed Feb 18, 1997* .

☒ The allowed claim(s) is/are *25 and 36-114* .

☐ The drawings filed on _____ are acceptable.

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE **THREE MONTHS** FROM THE "DATE MAILED" of this Office action. Failure to timely comply will result in ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

☒ Applicant MUST submit NEW FORMAL DRAWINGS

☐ because the originally filed drawings were declared by applicant to be informal.

☒ including changes required by the Notice of Draftsperson's Patent Drawing Review, PTO-948, attached hereto or to Paper No. 7 .

☐ including changes required by the proposed drawing correction filed on _____ , which has been approved by the examiner.

☐ including changes required by the attached Examiner's Amendment/Comment.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the drawings. The drawings should be filed as a separate paper with a transmittal lettter addressed to the Official Draftsperson.

☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any response to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 8

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☐ Interview Summary, PTO-413

☐ Examiner's Amendment/Comment

☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material

☒ Examiner's Statement of Reasons for Allowance

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DETAILED NOTICE OF ALLOWABILITY

1) This Office Action is in response to the amendment filed February 18, 1997, now paper #13, canceling claims 26-34, and adding claims 41-113, and the amendment faxed June 5, 1997 canceling claim 35 and adding claim 114. Currently, claims 25 and 36-114 are pending.

Restriction

2) The examiner finds the newly presented/amended claims to be in accordance with the elected Group I which was drawn to a method of treating undesired angiogenesis with the instant compounds wherein exactly one of R5, R6, and R8 is -N(Y)-R10 and R9 is formula A) having exactly one of R11-R16 is -N(Y)-R10.

Art Based Rejections

3) Claims 25, 26, and 34 were rejected under 35 U.S.C. 103(a) as being unpatentable over **Goihman-Yahr** (Goihman-Yahr, M. Et al, Int. Nac. Dermatol. 1978, 57(4), pages 317-32). The examiner finds the amendment to have canceled the obvious subject matter; therefore the rejection is **WITHDRAWN**.

4) Claims 25, 26, and 34 were rejected under 35 U.S.C. 103(a) as being unpatentable over **Hatfill** (Hatfill, S.J. et al, Leuk. Res. 1991, 15(2-3), pages 129-36). The examiner finds the amendment to have canceled the obvious subject matter; therefore the rejection is **WITHDRAWN**.

5) Claims 25, 26, and 34 were rejected under 35 U.S.C. 103(a) as being unpatentable over **Vogelsang** (see PTO-1449, paper #8). The examiner finds the amendment to have canceled the obvious subject matter; therefore the rejection is **WITHDRAWN**.

6) Claim 25, 26, and 34 were rejected under 35 U.S.C. 103(a) as being unpatentable over **Waters** (see PTO-1449, paper #8). The examiner finds the amendment to have canceled the obvious subject matter; therefore the rejection is **WITHDRAWN**.

7) Claims 25, 26, and 34 were rejected under 35 U.S.C. 103(a) as being unpatentable over **Mummery** (Mummery, C.L. et al, Toxicol. Lett. 1983, 18(3), pages 201-9, the online abstract has been solely relied upon for this rejection). The examiner finds the amendment to have canceled the obvious subject matter; therefore the rejection is **WITHDRAWN**.

8) Claim 25, 26, 33, 34, 36, 37, and 40 were rejected under 35 U.S.C. 103(a) as being unpatentable over **De** (De, A. U. et al, J. Pharm. 1975, 64(2), pages 262-6) in view of each of the references of **Folkman** (see PTO-1449, paper #8) and **Gimbrone** (see PTO-1449, paper #8). The examiner finds the amendment to have canceled the obvious subject matter; therefore the rejection is **WITHDRAWN**.

9) Claim 25, 26, and 34 were rejected under 35 U.S.C. 103(a) as being unpatentable over **Graudums** US 3,705,162 in view of **Folkman** (see PTO-1449, paper #8). The examiner finds the amendment to have canceled the obvious subject matter; therefore the rejection is **WITHDRAWN**.

10) Claim 25, 26, and 34 were rejected under 35 U.S.C. 103(a) as being unpatentable over **Gutierrez-Rodriguez** (Guiterrez-Rodriguez, O. et al, J. Rheumatol. 1989, 16(2), pages 158-63, the online abstract has been solely relied upon) in view of **Colville-Nash** (see PTO-1449, paper #8). The examiner finds the amendment to have canceled the obvious subject matter; therefore the rejection is **WITHDRAWN**.

11) Claims 25, 26, 34, and 36-40 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of 08/168,817, now US 5,629,**327**. The examiner finds the amendment to have canceled the obvious subject matter; therefore the rejection is **WITHDRAWN**.

12) Claim 35 was rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of 08/371,987, now US 5,593,**990**. The examiner finds the amendment to have canceled the obvious subject matter; therefore the rejection is **WITHDRAWN**.

13) Claim 34 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The examiner finds the amended claims to particularly point out and distinctly claim the subject matter which applicant regards as the invention; therefore, the rejection is **WITHDRAWN**.

14) Claims 28 and 29 were objected to for being dependent upon a rejected base claim. The examiner finds the objection moot, since the claims have been canceled, and as such the objection is **WITHDRAWN**.

REASONS FOR ALLOWANCE

15) Claims 25 and 35-113 are allowable over the prior art of record. **Jonson** (reference AT on the PTO-1449, paper #8) teaches the instant 3-aminothalidomide and 3-hydroxythalidomide as compounds 7 and 4 respectively on page 524. The examiner finds the claims, drawn to a method of treating undesired angiogenesis, allowable since Jonson limits his discussion of said compounds to their teratogenic properties and there is no teaching or suggestion within the prior art of record that the compounds would be useful in treating undesired angiogenesis.

16) **Muller** US 5,635,517 (filed 24 July 1996 and patented 03 June 1997) claims methods similar to the instant. The difference between the methods of Muller and the instant is the instant is drawn to a method of treating undesired angiogenesis by administering 3-aminothalidomide

and the reference is drawn to a method of reducing the levels of TNF-α (tumor necrosis factor) by administering 3-aminothalidomide The art shows that there is a relationship between TNF-α and angiogenesis, but the legal issue is whether it would be obvious to a skilled artisan that a compound which inhibits TNF-α would also inhibit angiogenesis. Neovascularization, vasculogenesis, and angiogenesis are terms which describe the process whereby new capillaries are formed. This process is very important during embryonic development, at ovulation during the formation of the corpus luteum, and during wound healing; however, many pathological disease states are characterized by increased angiogenesis including but not limited to diabetic retinopathy, neovascular glaucoma, psoriasis, and tumor growth. TNF-α is one of many factors that induce angiogenesis including: aFGF (fibroblast growth factor), bFGF, TGF-α (transforming growth factor), VPF, or VEGF (vascular endothelial growth factor), monobutyrin, angiotropin, angiogenin, hyaluronic acid degradation products, and AGE-products. **Fajardo** (Fajardo, L.F. et al, Am. J. Pathol. 1992(Mar), 140(3), pages 539-44, abstract only) teaches that low doses of TNF induce angiogenesis; however, high doses of TNF inhibit angiogenesis. **Hu** (Hu, D.E. et al, Inflammation, 1994(Feb), 18(1), pages 45-58, abstract only) discloses that the administration of TNF-α caused intense neovascularization in a rat sponge model; however, in the absence of exogenous cytokines, the sponge-induced angiogenesis was not modified by the TNF-α antibody alone. **Montrucchio** (Montrucchio, G. et al, J. Exp. Med. 1994(July 1), 180(1), pages 377-82, abstract only) teaches the angiogenic effect of TNF-α is atleast in part mediated by PAF (platelet activating factor) synthesized from monocytes and/or endothelial cells infiltrating the vehicle for

the delivery of the mediators, ie., the Matrigel plug. **Phillips** (Phillips, G.D. et al, Anatomical Record, 1996(May), 245(1), pages 53-6, abstract only) discloses that the TNF-α failed to elicit capillary formation in the rabbit cornea at all concentrations tested. There are several references showing that specific compounds shown to inhibit TNF-α also inhibit angiogenic activity. **Leibovich** US 4,808,402 discloses in example 5 of column 12, the antibody to TNF-α inhibits angiogenic activity produced by activated macrophages in culture; however, **Leibovich** concludes, in lines 60-62 of column 12, from the experiment, "[T]hat the macrophage-derived angiogenic agent is either identical or immunologically closely related to TNF-α," leaving open the possibility that the angiogenic agent may not be TNF-α. **Mongelli** US 5,260,329 discloses specific ureido derivatives which inhibit both TNF-α and angiogenesis; however **Mongelli** does not teach or suggest that compounds which inhibit one apriori inhibit the other, as evidenced by **Mongelli** performing separate experiments, see column 5 line 59 to column 6 line 2. Thus the Examiner concludes that a skilled artisan would find it "obvious to try" 3-aminothalidomide for angiogenic inhibition activity given the disclosure of **Muller '517**, but the test for obviousness under section 103 is greater than the "obvious to try" standard as adopted by the Federal Circuit as set forth in In re O'Farrell, 7 USPQ2d 1673 (CA FC 1988); therefore the claimed invention of **Muller '517** is patentably distinct from the instant.

17) The drawings remain objected to by the Draftsperson under 37 CFR 1.84 or 1.152, see the attached form PTO 948. Correction is required.

18) Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

19) Any inquiry concerning this communication or earlier communications from the examiner should be directed to Garth Dahlen, Ph.D. whose telephone number is (703) 308-4608.

GMD

June 9, 1997

C. WARREN IVY
SUPERVISORY PRIMARY EXAMINER
GROUP 1200